REMARKS

Claim Status and Amendment to Claims

Claims 14, 16, 17, 22, 23, 25, 26, and 28-44 were pending in the present application. Claims 14, 16, 17, 22, 23, 25, 26, 28-39, and 41-44 are hereby canceled. Claim 40 is hereby amended. New claims 45-53 are hereby presented. Support for the amendment and new claims may be found throughout the original specification and claims. No new subject matter has been introduced.

The claims in the present application have been amended to more closely match those in related, pending application 12/579,302 (the "'302 application"), which is directed to methods of detecting the presence of an analyte using a fluorescent silica-based nanoparticle

Double Patenting

Claims 14, 16, 22-24, 26, 28, and 31 are provisionally rejected over claims 48, 60, 62, 64, and 66 of co-pending application 10/306,614 (the "'614 application").

The provisionally rejected claims have been canceled. With respect to the pending claims, Applicants note that the '614 application is abandoned. A continuation of the '614 application, the above-mentioned '302 application, is currently pending. The '614 application is the earlier filed application, as compared to the '302 application.

To the extent that a double patenting rejection in view of the pending '302 application applies to the pending claims, Applicants request that it be held in abeyance pending disposition of any other rejections. Should the double patenting rejection remain the only pending rejection, Applicants request that the rejection be withdrawn and this application, as the earlier filed application, be allowed to issue in accordance with MPEP 804.I.B.1.

Anticipation- Trau

Claims 14, 16, 17, 22, 23, 25, 26, 28-32, and 34-38 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Pat. Pub. 20030124564 (hereinafter "Trau").

The rejected claims have been canceled, rendering the rejection moot as to those claims. Applicants hereby address the relevance of Trau to the patentability of the pending claims, particularly with respect to the diameter of the claimed nanoparticles.

Trau does not teach or suggest particles having diameters of 70 nm or less, with cores that comprise an organic functional group having a mercapto substituent and a fluorescent compound

In the Office Action at page 7, citing to paragraphs [0088] and [0019] of Trau, the Examiner stated that Trau teaches nanoparticles having diameters of 80nm or smaller. Applicants assert that Trau fails to teach nanoparticles having a core as claimed, with diameters of 70 nm or less.

Applicants note that the two paragraphs cited by the Examiner, discuss two very different types of particles discussed in Trau, neither of which read on the claimed compositions.

Trau at [0088]- small, Stober particles

In paragraph [0088], Trau discusses a core synthesized via the Stober process. As acknowledged by Trau, the Stober process yields a monodisperse particle of silica, without the claimed fluorescent compound or mercapto substituent in the core. *See* Trau at [0009] and [0008]. It is these silica-only Stober cores that Trau, at [0088], teaches as having diameters as small as 20 nm. However, these cores clearly do not incorporate an organic functional group having a mercapto substituent or a fluorescent compound. Rather, a fluorescent compound is added only after formation of the core and prior to the addition of a clear silica shell. Trau at [0088]. In the context of Trau, these smaller, fluorescent particles are used as "tagging particles" or "beads" in

conjunction with larger, porous "carrier particles." Trau at [0088] and [0094]. It is these larger, porous "carrier" particles that are the main focus of Trau. Trau at Abstract.

Trau at [0019]- large, porous particles

In paragraph [0019], Trau discusses larger, porous particles having a minimum size of 80 nm for the core alone. Trau does teach that these larger, porous particles may incorporate fluorescence in their cores. Paragraph [0019] is best understood with respect to paragraph [0094], which makes clear that the 80 nm core was only achieved through the addition of size-reducing detergent. To arrive at the core-shell particles of the claims, a silica shell must be added to the 80 nm core. Trau cites to van Blaaderen for methods of forming the shell. Trau at [0085]. However, the smallest silica shell thickness reported in the cited van Blaaderen article is 9 nm. Accordingly, even at the lowest range, Trau only teaches core-shell particles having cores with incorporated fluorescence and a total particle diameter of 98 nm or greater (80 nm core + 2 times 9 nm shell thickness).

Therefore, Trau does not teach particles having core-shell architecture, an organic functional group having a mercapto substituent and a fluorescent compound both incorporated in the core, and particle diameters of 70 nm or less, as claimed. Rather, the smallest particles of Trau do not have a fluorescent compound in their core (Trau at [0088]) and the smallest core-shell particles with fluorescent cores are 98 nm in diameter, or greater (Trau at [0019]).

No rationale to modify Trau to arrive at the claimed method

As discussed above, Applicants assert that Trau does not teach or suggest the claimed nanoparticles. Applicants further assert that there would be no rationale to modify the teachings of Trau to yield a core-shell nanoparticle of 70 nm or less. Further, core-shell particles having a diameter with 70 nm or less would be unsatisfactory for the intended purpose of Trau, pursuant to MPEP 2143.01.V.

Trau, in fact, teaches away from smaller particles in favor of larger particles. Trau states that its particles are intended for use in flow cytometer applications,

particular for use with DNA synthesizers, both applications requiring particles of typically greater than 2 microns (2000 nanometer) in diameter. Trau at [0004], [0008], [0039], claim 1, and claim 25. Additionally, Trau describes a need for particles with a large number of surface binding sites and/or high porosity. Trau at [0016]. As outlined in the first paragraphs of the "Detailed Description of the Invention" section, these goals could be accomplished by moving away from silica forming moieties like tetraethyl orthosilicate (TEOS) to silane derivative coupling agents like 3-mercaptopropyl trimethoxysilane (MPS) or 3-aminopropyl trimethoxysilane (APS). Trau at [0060], [0061] and [0066].

MPEP 2143.01.V. states that the proposed modification cannot render the prior art unsatisfactory for its intended purpose. Applicants assert that one of skill in the art would not find it obvious to modify the particles of Trau in a manner that would render them unsatisfactory for their intended use as supports for flow cytometer applications. Only impermissible hindsight would lead one of skill to attempt to modify the particles of Trau in a manner that would render them unsuitable for use as supports in DNA synthesis and flow cytometery. This purpose is confirmed by Trau's teachings away from the use of small particles. Trau at [0008] ("Unfortunately, commercially available silica particles typically are limited to less than 5 microns diameter size. Such sizes are too small for many flow cytometer applications and for use in machinery such as a conventional DNA synthesizer") and [0013] ("Unfortunately, particles formed via the Stober process generally are limited to a maximum size of approximately 3 microns, which is insufficient for many purposes."). While Trau teaches the limited use of small, Stober particles in paragraph [0088], discussed above, these particles are inserted into the pores of larger, porous particles for actual use. Trau at [0088] and [0094].

Applicants therefore assert that a person of skill would have no rationale to modify Trau, singly or in view of other references, to yield core-shell particles with an organic functional group having a mercapto substituent and a fluorescent compound both incorporated in the core, and diameters of 70 nm or less.

No reasonable expectation of success in modifying the particles of Trau to arrive at the claimed composition

As discussed above, the smallest Trau core-shell particle having an organic functional group having a mercapto substituent and a fluorescent compound both incorporated in the core is 96 nm in diameter, at the smallest. Trau at [0094]. This particle size was only obtained through the use of size-reducing detergents. Trau provides no guidance as to how to achieve particle sizes having the claimed core composition smaller than this minimum size. Trau specifically teaches that incorporation of its silane coupling agent increases particle size. Trau at [0060]. A person of ordinary skill in the art would not have an expectation of success in synthesizing small diameter particles having the diameters of the present claims.

To the extent this rejection applies to the pending claims, Applicants respectfully request that the rejection be withdrawn.

Obviousness- Trau in view of van Blaaderen

Claims 14, 16, 17, 22, 23, 25, 26, 28-32, and 34-44 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Trau in view of van Blaaderen *et al.* (The Colloid Chemistry of Silica, Chapter 4, pp. 84-111; Advances in Chemistry. Vol. 234; 1994) (hereinafter "van Blaaderen 94").

Rejected claims 14, 16, 17, 22, 23, 25, 26, 28-32, 34-39, and 41-44 have been canceled, rendering the rejection moot as to those claims. Applicants hereby address the applicability of the rejection to remaining rejected claim 40 and newly added claims 45-53.

Applicants refer to the discussion of Trau, as discussed above. Applicants again assert that Trau does not teach a core having a mercapto substituent and a fluorescent compound of diameter of less than 80 nm. Even if this core were to be combined with the smallest shell taught by van Blaaderen 94, the smallest particle diameter yielded would be 98 nm.

Also as discussed above, one of skill would have no rationale to modify Trau to arrive at the claimed particles or any expectation of success in doing so. Rather, one of

skill would recognize that doing so would render the particles of Trau unsuitable for their intended purpose and therefore not obvious.

Applicants note that the Examiner mentions the teachings of van Blaaderen 94 concerning particles having diameters as small as 18 nm. However, like the particles of [0088] of Trau, these van Blaaderen 94 particles do not have the core composition of the claimed particles. The particles of van Blaaderen 94 are TES (tetraethoxysilane)-only particles, Stober particles, and TES and APS (3-aminopropyltriethoxysilane) particles without fluorescent dyes in their cores or mercapto substituents. van Blaaderen 94 at pages 94-95 ("The first step was the synthesis of several colloidal systems with different radii from TES alone . . . . The second step consisted of the coating of several 'Stöber' silica particles with APS and the synthesis of a new kind of particles from a mixture of APS and TES.")

To the extent this rejection applies to the pending claims, Applicants respectfully request that the rejection be withdrawn.

Obviousness- Trau in view of van Blaaderen and further in view of Gu

Claims 14, 16, 17, 22, 23, 25, 26, and 28-44 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Trau in view of van Blaaderen 94 and further in view of U.S. Pat. Pub. 20020048800 (hereinafter "Gu").

Rejected claims 14, 16, 17, 22, 23, 25, 26, 28-39, and 41-44 have been canceled, rendering the rejection moot as to those claims. Applicants hereby address the applicability of the rejection to remaining rejected claim 40 and newly added claims 45-53.

Applicants assert that the addition of Gu does not address the issues raised with respect to Trau alone or Trau and van Blaaderen 94. Rather, it appears that the Examiner cites to Gu purely for its disclosure with respect to reagents for fluorescently labeling biological molecules. As such, Applicants believe that it cannot overcome the defects of Trau, particularly with respect to particle diameter. Applicants reserve the

right to address Gu in detail, particularly with respect to the dependent claims, if needed.

To the extent this rejection applies to the pending claims, Applicants respectfully request that the rejection be withdrawn.

Obviousness- van Blaaderen 92 and others

Claims 14, 16, 17, 22, 23, 25, 26, and 28-44 are rejected under 35 U.S.C. § 103(a) as being unpatentable over van Blaaderen *et al.* (Langmuir. Vol. 8: 2921-2931; 1992) (hereinafter "van Blaaderen 92") in view of van Blaaderen and further in view of Gu and Melde *et al.* (Chem. Mater. Vol. 11: 3302-3308; 1999) (hereinafter "Melde").

Rejected claims 14, 16, 17, 22, 23, 25, 26, 28-39, and 41-44 have been canceled, rendering the rejection moot as to those claims. Applicants hereby address the applicability of the rejection to remaining rejected claim 40 and newly added claims 45-53.

As an initial matter, Applicants note that van Blaaderen 92 was cited and discussed (and later withdrawn) at length in the prosecution of the parent '614 application. *See e.g.*, '614 application prosecution at Office Action of September 25, 2006 and Response of December 22, 2006. Applicants realize that the '614 application is separate from the present application. Nonetheless, Applicants are surprised to find a reference that has been extensively considered being recycled for essentially the same rejection.

As Applicant noted in various responses in the prosecution of the '614 application, that the diameter of the particles in van Blaaderen 92 was no smaller than 280 nm. *See* van Blaaderen 92 at Table III. Notably, that 280 nm diameter particle is for a particle of system "1B." *Id.* As evident from Figure 1, system "B" particles do not have fluorescent dye groups in their core, as claimed. Rather, the only system type having a dye labeled core and a silica shell is system "F." The smallest system "F" particle disclosed in van Blaaderen 92 is 980 to 1000 nm. *See* van Blaaderen 92 at Tables I and III. Accordingly, van Blaaderen 92 discloses particles substantially larger

than those of the present claims, particularly for particles having fluorescent dyes in their core. Applicants also note that van Blaaderen 92 does not disclose cores having mercapto substituents, as required by the present claims.

With respect to modifying the size of the van Blaaderen 92 molecules through the teachings of van Blaaderen 94, Applicants respectfully assert that one of skill understands that core composition and size are not independent features that may be simplistically swapped from one particle to another. Rather, the two are intimately linked. Accordingly, one of skill would not consider it predictable or obvious that the large cores of van Blaaderen 92 could be made with diameters of 70 nm or less simply because another reference (*i.e.*, van Blaaderen 94) teach core sizes of 18 nm though clearly with different core compositions.

To the extent this rejection applies to the pending claims, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-0289** referencing **Docket No. 1258_3378US**.

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Enclosures